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Review

Opportunities for Chiral Agrochemicals*

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Abstract: Chiral compounds account for 25% of all agrochemical compounds used commercially and for 26% of the total value of the world agrochemical market. However, those sold in single isomer form contribute only 7% to the market value despite many potential advantages in terms of regulatory, intellectual property and marketing benefits. Limited access to chiral raw materials and economic synthesis routes are key reasons why single isomers are less common than they might be. The development of more chiral routes will encourage the development of single isomer compounds to capitalise on their advantages.

Key words: agrochemical, chiral, isomer.

1 INTRODUCTION

Most chemical reactions make no distinction between pairs of molecules which are chiral isomers; both are normally present and both normally react to produce chemically the same product which is the racemic mixture, or racemate.

Many compounds used in the pharmaceutical and agrochemical industries contain chiral centres and are produced, and used as racemic mixtures. But, when applied, they are engaged in biochemical interactions and receptors generally distinguish between chiral pairs. In some cases the activity difference between the two isomers is not great, perhaps because the chiral centre is not intimately involved in the binding, while in others it can be considerable.

If there are two isomers the consequences of different activities between them are:

- half the product may be useless, while costs have been incurred in its production;
- half of the product poses a load on the system to which it is applied; resources have to be devoted to its removal;
- half of the product may react with a different cellular receptor and may cause an unwanted, and potentially damaging, side-effect.

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The situation is of course more complex if the molecule has two or more chiral centres in which case there are more isomers—specifically 2^n isomers for n chiral centres.

An analysis by Ariens[1] in the 1980s suggested that 19% of agrochemicals then in use were chiral molecules. Despite several of these having been withdrawn from use subsequently, the proportion is now 25%

2 WHY CHIRAL AGROCHEMICALS ARE BECOMING MORE COMMON

There are several reasons why chiral agrochemicals are becoming progressively more common; the main ones are:

- In the earlier days of the agrochemical industry the search for new active ingredients began with relatively simple molecules, including inorganics (e.g. the copper fungicides) and very simple organic molecules. Essentially, all such molecules have now been evaluated. As a result, it is inevitable that newer compounds will have complex molecular structures which are more likely to contain stereochemical variations, including chirality.
- Individual new compounds which are chiral have been introduced because they have been found to be effective in conventional empirical screening programmes. Commercially successful introductions have led the originating companies, and others, to try to develop related compounds and, of

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course, these will also tend to be a chiral. An example is the commercial success of triadimefon which started the search for other triazole fungicides, of which there are now 23 examples in use or in the late stages of development. In common with diclobutrazole, it also provided leads for plant growth regulators.

- Researchers have increasingly looked to naturally occurring products, which are usually chiral, as a source of ideas for new compounds. Success with one compound has led to increased efforts by other companies. Elliott's success with the synthetic pyrethroids, which are based on the natural pyrethrins, is the most obvious example.
- Our understanding of biochemical pathways has developed enormously in recent years. This has led to attempts to design molecules so that they fit identified cellular receptors. Since such receptors are themselves chiral, it is likely that such 'designed' molecules will also be chiral. However, the number of compounds discovered in this way and developed successfully has been negligible so far.
- The understanding of pest biochemistry and metabolic pathways of pesticides in target pests has, however, been fruitful in another way. Such understanding enables companies to create screens which operate at cellular level rather than whole organism level. Consequently, researchers are able to observe more subtle effects of a candidate compound than is possible in conventional screens. Since they are observing chiral biochemical systems there is likely to be a greater chance that the 'successful' compounds are themselves chiral.

3 THE DRIVING FORCES FAVOURING THE ADOPTION OF SINGLE ISOMERS

There are regulatory, intellectual property, marketing and profitability factors which tend to favour the adoption of single isomers or, in some cases, enhanced isomeric constitution.

3.1 Regulatory factors

Differential biological activity patterns between isomers means that regulatory authorities may wish to be assured that none of the components of a racemic mixture generates side-effects. Pharmaceutical regulators, especially the Food and Drug Administration (FDA) of the USA, are active in this area.

In the case of agrochemicals, a primary consideration for regulatory authorities, and therefore for agrochemical manufacturers, is assurance that the agrochemical product achieves a satisfactory degree of selectivity between the target and all other species with which the product comes into contact. Should there be reason to suppose that the two isomers of a racemic mixture have different degrees of selectivity (including especially the cases where one is ineffective, antagonistic or its mode or site of action is different), there is likely to be regulatory pressure on the manufacturer to produce only the isomer with the more favoured profile.

Regulatory concern has so far been largely directed towards the environmental consequences of the application of a substance which is inactive for the desired purpose but poses an additional loading on the environment. Thus, the authorities in The Netherlands and Switzerland have revoked registrations for racemic mixtures of chiral phenoxy herbicides, whilst approving registrations of single-isomer products.

In addition to direct regulatory action of the type noted in relation to the aryloxyalkanoic acid (phenoxy) herbicides, the authorities in several countries have announced plans aimed at reducing the volumes of agrochemicals used. The Netherlands, Sweden and Denmark have announced their aim to achieve reductions of as much as 50% over a 10 year period. In addition, Sweden has implemented a tax on agrochemicals based on the weight of active ingredient and other countries are believed to be considering this approach. Therefore, regulatory considerations can generally be expected to favour manufacturers switching from racemates to single isomers and developing new active ingredients as single isomers in preference to racemates. In extreme cases, approval may not be forthcoming unless this is done.

3.2 Intellectual property

Agrochemical manufacturers are dependent upon intellectual property rights (IPR) to allow them a period of time in which to recoup the investment made in the development and introductory phases of a new product. With the long lead times from discovery to commercialisation (typically 10 years or more), heavy developmental expenditure during that time, including that of obtaining regulatory approval, and considerable investment in manufacturing plant and launch marketing costs, agrochemical companies use patents to give themselves a period for exclusive exploitation of the products they have developed. Strategies for extending that period offer a significant economic return before the franchise of the developer is threatened by manufacturers of generic products. Accordingly, agrochemical companies seek a variety of strategic approaches to maintain their franchise in the face of such competition. The filing of later process patents, maintainable after the expiry of product patents, is one approach that has given benefits to some companies in some markets.

Thus, re-registering an agrochemical in a single-isomer form and obtaining a unique ability to manufac-

ture that form, perhaps by patenting the process or a key intermediate, would be a way of effectively extending the patent life of a valuable compound. Roussel-Uclaf has used this approach to ensure that it will be able to maintain a dominant position with the leading synthetic pyrethroid, deltamethrin, for some years after the expiry of the core NRDC patent covering it as a product.

3.3 Marketing factors

A single-isomer product offers the possibility of a company establishing marketing advantages which will help it to achieve a stronger competitive position. Marketing factors favouring the adoption of single isomers include:

- the 'green' image of a product applied at a lower dose rate and therefore being kinder to the environment;
- more effective use of the product because the farmer can spray more of a crop with a given quantity of a single isomer as compared with the racemate;
- less bulky product, saving packaging costs and freight and storage costs at all stages of the distribution channel.

3.4 Profitability

In manufacturing a racemic mixture, costs are incurred in raw materials, manufacturing overheads and packaging for the inactive form. So, if only the active form is manufactured, there are potentially substantial cost savings. The degree of saving may be reduced if the chirally defined intermediate is itself more expensive than the original intermediates used in the racemic synthesis or requires the route to be altered. It is the interplay between the different raw material costs in the two cases which will determine the degree of cost saving achieved by adopting the single isomer as the preferred product.

The cost saving will therefore vary between active ingredients, but could be as much as 50%. A further impact on profitability comes from the price per unit of product that can be obtained. If the single-isomer product is twice as active as the racemate, the price per kilo ought to be twice as high. Allowing for various marketing advantages, a substantial premium over that price may be achievable.

A major investment for an agrochemical company is in manufacturing plant. Plants are often specific to an individual compound, although re-piping etc. sometimes makes it possible to treat them as general purpose plants. The gain in capital cost from manufacture of an agrochemical in single-isomer form will vary for each active ingredient. In the case of an established product, switching from a racemic mixture to a single isomer may be a way of doubling capacity with little extra expenditure on manufacturing plant, depending upon the availability of the correct intermediates. The point at which a single isomer is introduced into the process will influence the ability of the manufacturer to use all or part of an existing plant to produce the single-isomer end-product. In the case of a new compound, designing the plant for a single-isomer product may allow a smaller plant to be built, at lower cost, or a plant with larger capacity, in terms of useful product, at similar cost.

4 THE RESTRAINING FORCES LIMITING THE ADOPTION OF SINGLE ISOMERS

Practical and economic issues presently limit the ability of manufacturers to introduce single-isomer products. Economic manufacture of a single isomer depends upon availability of the appropriate building blocks and reaction sequences. It is certain that the full panoply of these has not yet been defined and/or economically optimised. This adversely impacts both the revenue side (expensive intermediates) and the capital side (more complex plant). In time, it is realistic to expect many new developments, driven perhaps by increasing requirements by the pharmaceutical sector. The emphasis on the subject shown in recent patent literature and the creation of several specialist chiral companies suggest that considerable progress will be achieved in the next few years.

5 THE PRESENT COMMERCIAL POSITION

Examples of chiral molecules exist in many classes of agrochemical compounds. In each of the following classes, chiral molecules are relatively common:

Herbicides: phenoxys, oxyphenoxypropionates, cyclohexanediones, imidazolinones
Insecticides: synthetic pyrethroids, organophosphates
Fungicides: triazoles, morpholines

In addition, there are examples of chiral molecules in a large number of other classes, even though the majority of current compounds in these classes do not exhibit the phenomenon. Finally, it should be noted that all naturally derived compounds (e.g. the fungicides blasticidin S, kasugamycin and polyoxin B) are chiral.

A survey of the commercial importance of all agrochemical compounds with chiral centres was carried out by the author in 1992, in the course of preparing a report,[2] based on the compounds then listed in the

TABLE 1
Commercial Significance of Chiral Agrochemical Compounds and the Number of Compounds in each Sector[a]

	Number of chiral compounds in category (group)			*Total chiral compounds*	*Total number of compounds assessed*
	A[b]	*B*[b]	*C*[b]		
Herbicides	9	17	17	43	198
Insecticides	5	20	31	56	220
Fungicides	5	19	19	43	147
Plant growth regulators/Others[c]	0	1	13	14	14
Total	19	57	80	156	626

[a] Based on a survey carried out in 1992 by the author and updated for this paper.
[b] See text for description of classification.
[c] Includes molluscicides, bird repellents, safeners but excludes rodenticides.

Pesticide Manual;[3] this survey was updated in the course of preparing the present paper. The chiral agrochemical compounds have been classified into three groups depending on their commercial significance:

A. commercially important; their current sales levels are estimated to be in excess of US $100 million per annum;
B. commercially significant; their current sales levels are estimated to be in the range US $25–100 million per annum;
C. commercially not very significant; their sales levels are estimated to be below, often much below, US $25 million per annum and several of them are declining.

As a general rule, the greater the significance of an existing compound, the greater interest manufacturers are likely to have in switching to a single-isomer form. The broad suggestions for each classification are:

A compounds: There is likely to be commercial merit in these compounds being marketed as single isomers, provided that an economic synthetic route can be defined.
B compounds: There may be merit in transferring to a single isomer, although it seems more likely that this will be done to prevent regulatory withdrawal rather than for other reasons.
C compounds: Unlikely to be transferred to single isomers; the response to a regulatory threat is more likely to be withdrawal of the compound.

For newer compounds, manufacturers will base their decisions on the anticipated sales level.

The survey indicates that of the 156 chiral compounds identified, only 19 (including nine herbicides) can be classified as commercially important while 80 (including most naturally derived compounds) are not commercially significant on a world scale, although a few have strong positions in relatively small niche market sectors (Table 1). The same table shows that insecticides contribute the greatest number of chiral molecules; in large measure this is the result of the importance of the synthetic pyrethroids. The table also shows the total number of agrochemical compounds in each sector. About 25% of all agrochemical compounds are chiral; the proportion is slightly higher in fungicides and slightly lower in herbicides.

Table 2 lists the chiral agrochemical compounds which are classified as commercially important. While the nine herbicides come from a number of classes, the synthetic pyrethroids dominate the insecticides category and the triazoles dominate the fungicide category. Of the total number of chiral compounds, only 28 are marketed as single-isomer products or as mixtures containing an enhanced proportion of the most active enantiomer. Table 3 lists these compounds, of which 16 are manufactured by synthetic routes while 12 are derived biologically.

TABLE 2
Commercially Important Chiral Agrochemical Compounds

Herbicides	*Insecticides*	*Fungicides*
Dichlorprop	Cyhalothrin	Flutriafol
Mecoprop	Cypermethrin	Propiconazole
Glufosinate	Deltamethrin	Tebuconazole
Fluazifop	Fenvalerate	Triadimefon
Haloxyfop	Malathion	Fenpropimorph
Sethoxydim		
Imazamethabenz		
Imazethepyr		
Metolachlor		

TABLE 3
Chiral Agrochemical Compounds Sold as Single Isomers or as Enhanced Isomeric Mixtures

Herbicides	*Insecticides*	*Fungicides*	*Plant Growth Regulators*
Mecoprop	Deltamethrin	Blasticidin S	Gibberellic acid
Dichlorprop	Cypermethrin	Kasugamycin	
Fluazifop	Cyhalothrin	Pimaricin	
Haloxyfop	Fenvalerate	Polyoxin B	
Fenoxaprop	Allethrin	Streptomycin	
Quizalofop	Cyfluthrin	Validamycin	
Flamprop	Taufluvalinate		
Propaquizafop	Tetramethrin		
Bilanophos	Abamectin		
	Nicotene		
	Pyrethrins		
	Rotenone		

To assess the commercial contribution made by chiral molecules and by those sold as single isomers or sometimes, like allethrin, as enhanced isomeric mixtures, Table 4 has been constructed. This table shows the value of the total agrochemical market for each sector, the value of compounds in each sector which are chiral and the value of those which are sold in single-isomer, or enhanced, form; more than half the value of single isomers is in insecticides.

Table 5 looks at the relative importance of chiral compounds in the different market sectors. Overall, chiral compounds account for 25% of all agrochemical compounds and 26% of the total agrochemical market value, but those compounds sold as single isomers account for only 7% of the total market value. Interestingly, the first two columns show that the number of chiral molecules and their contribution to the total market are quite consistent; in other words chiral molecules are, on average, as commercially successful as non-chiral molecules. However, a very different picture is found when comparing the last two columns. Single-isomer compounds make much the greatest contribution in insecticides, a minor contribution in herbicides and a negligible contribution in fungicides. In the case of insecticides, the influence of the synthetic pyrethroid group is obvious.

TABLE 4
Commercial Significance of Chiral Agrochemicals: All Values Shown for 1993 in US$M at End-User Level

	All compounds	*Chiral compounds*	*Compounds sold as single isomers*
Herbicides	11275	2500	570
Insecticides	6990	2330	1075
Fungicides	4415	1285	60
Plant growth regulators/Others	1420	170	20
Total	24100	6285	1725

TABLE 5
Percentage Contribution of Chiral Compounds to the Number of Agrochemical Compounds and to Market Value

	Chiral compounds		*Single-isomer formulations*[a]
	Number	*Value*	*Value*
Herbicides	22	22	5
Insecticides	25	33	15
Fungicides	29	29	1
Plant growth regulators/Others	23	12	1
Total	25	26	7

[a] Includes compounds sold in enhanced isomeric mixtures.

6 COMMENTS ON KEY CHIRAL GROUPS

6.1 Herbicides

Single isomers have been adopted primarily in the phenoxy group and the oxyphenoxypropionates. Some of the recent market recovery in the former class has been attributed to the introduction of chiral forms of dichlorprop and mecoprop, first by BASF in 1987. In these two compounds which contain chiral centres, only one form is active while the other is totally inactive. Thus, there is a clear opportunity to reduce environmental loading and it has been taken by regulatory

authorities in The Netherlands and Switzerland. For marketing reasons, companies have now introduced the single-isomer form in several other countries.

6.2 Insecticides

The synthetic pyrethroids have more complex molecules than most agrochemical compounds. Each of the commercialised pyrethroids contains two or three chiral centres, so that there are four or eight isomers in each case. All the leading compounds have been introduced in resolved form; particular note needs to be made of deltamethrin, the leading compound, which exists in eight isomers but which is sold exclusively as the most active isomer. Deltamethrin contributes nearly one-third to the total value of insecticides sold as single isomers.

6.3 Fungicides

There have been no commercial introductions of single isomers of the triazoles. This is interesting because there is a fine line between their being fungicides or plant growth regulators and it appears that this variation may be induced by the chiral part of the molecule; indeed three triazole compounds (paclobutrazole, triapenthenol and uniconazole) are actually marketed as growth regulators and the commercial success of diclobutrazole as a fungicide was hampered because of its growth-regulating side-effects, with the fungicidal and growth-regulating effects being concentrated in different isomers. The impact of chirality on activity is less clear with the triazole fungicides than with the pyrethroid insecticide and phenoxy herbicide classes. In most cases, the activity of the different isomers (generally two but sometimes four) is not specifically stated in sources such as the Pesticide Manual[3] and a racemate is normally marketed. However, cyproconazole and diniconazole are implied to have differential activity between their isomers by the fact that they each have two CAS registration numbers.

7 COMPANIES INVOLVED IN CHIRAL CHEMISTRY

A large number of companies are now active in chiral chemistry. Amongst the agrochemical manufacturers the following may be noted: BASF, DowElanco, Hoechst, A. H. Marks, Rohm & Haas, Roussel-Uclaf, American Cyanamid, Sumitomo and Zeneca.

Intermediate suppliers to the industry, or to the pharmaceutical industry, who are active in chiral chemistry include Ajinomoto, Akzo Chemie, ARCO, Asahi, Boehringer Ingleheim, Boehringer Mannheim, Chemie Linz, Daicell, DSM/Andeno, Degussa, Enichem, Ethyl Corp, Ferruzi/Cerestar, FMC, Genzyme, Gist Brocades, ICI Fine Chemicals, Kanegafuchi, Kuraray, Kyowa Hakko Kogyo, Lonza, Mitsubishi Kasei, Showa Denko, Suntory and Synthelabo.

In addition, the last few years have seen the establishment of a number of, so far mostly small, companies, which specialise in chiral chemistry, although some have other activities as well. They include: Biocatalysts, Celgene, Chiron AS, Chiroscience, Creative Biomolecules, Oxford Asymmetry and Sepracor.

Finally, it should be noted that there are many active academic researchers, in a large number of universities, seeking new routes and building blocks. There are often collaborative associations between the specialist companies and these researchers.

8 THE IMPLICATIONS OF CHIRALITY FOR FUTURE AGROCHEMICAL INDUSTRY DEVELOPMENTS

This subject is considered for the cases of new compounds and existing compounds.

- For new compounds which are chiral, it appears to be increasingly common practice for the developer to investigate the difference in activity between the isomers. The literature carries many references to such investigations of the isomers of chiral compounds that are under development. The potential gain in capital cost, and in intermediate usage, is attractive in most chemical classes and introductions in single-isomer form, or in atypical ratios, such as in the case of pyrethroids, are to be expected, provided that economic chiral routes can be found.
- For existing compounds, there are potential gains to be made by switching from the present racemic mixtures. The factors encouraging a switch have been discussed above. Regulatory action directed at individual compounds (e.g. phenoxys), or at high-dose products through taxes, can be expected to lead to switching. Patent extension and marketing factors are also likely to encourage switching if one isomer is much less active than another; an example appears to exist in the oxyphenoxypropionates, where most members of the class are marketed in single-isomer form. However, the decision of a manufacturer to make the switch will depend upon the balance of the cost incurred and the commercial gain which is achievable. It is suggested that a switch is most likely to occur with those compounds which are commercially important, and much less likely with those which have a small or declining franchise.

However, it is also notable that there are classes of compounds which may not feature single-isomer introductions for many years, if at all. Those organophosphate insecticides which have the phosphorus atom as the chiral centre are examples where appropriate economic technologies do not seem to be available at present. Such technologies appear not to be required in pharmaceuticals and this may restrict the development effort. This contrasts with the situation where carbon is the chiral centre and where needs in the pharmaceutical industry may drive chiral synthesis development faster, to the benefit of the agrochemical industry.

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